Macromolecules **2004,** *37,* 9761−9767

Preparation and Characterization of Thermally Responsive and Biodegradable Block Copolymer Comprised of PNIPAAM and PLA by Combination of ROP and RAFT Methods

Yezi You,*,† Chunyan Hong,‡ Wenping Wang,† Weiqi Lu,‡ and Caiyuan Pan‡

Department of Polymer Materials and Engineering, College of Chemical Engineering,
Hefei University of Technology, Hefei, 230009, Anhui, People's Republic of China, and
Department of Polymer Science and Engineering, University of Science and Technology of China,
230026, Anhui, People's Republic of China

Received July 28, 2004; Revised Manuscript Received October 10, 2004

ABSTRACT: A special kind of reversible addition−fragmentation chain transfer (RAFT) agent with two ending hydroxy groups, S, S′-bis(2-hydroxyethyl-2′-butyrate) trithiocarbonate (BHBT), was successfully synthesized by using polymeric supports. BHBT can act not only as initiating centers in polymerization of lactide with tin(II) 2-ethylhexanoate catalyst but also as an efficient chain transfer agent in RAFT polymerization. The thermally sensitive and biodegradable block copolymers, poly(lactide-*b*-*N*-isopropylacrylamide-*b*-lactide) (PLA-*b*-PNIPAAM-*b*-PLA), were successfully synthesized by ring-opening polymerization (ROP) of lactide initiated from two hydroxy groups of BHBT and then RAFT polymerization of *N*-isopropylacrylamide (NIPAAM) using PLA with a centered trithiocarbonate unit as RAFT agent. The results of ^{1}H NMR and GPC analyses show that the triblock copolymer of PLA-*b*-PNIPAAM-*b*-PLA with well-defined structure and controlled molecular weight has been prepared by combination of ROP and RAFT methods. The aqueous solution of the micelles prepared from block copolymers using a dialysis method showed reversible changes in optical properties: transparent below a lower critical solution temperature (LCST) and opaque above the LCST.

Introduction

Synthesis of amphiphilic block copolymer with well-defined macromolecular architecture and controlled molecular weight is an attractive theme of research in polymer chemistry since amphiphilic block copolymers with both hydrophilic and hydrophobic segments have potential applications in molecular scale memory, photorefractives, displays, sensing, and drug delivery.[1−15] Poly(*N*-isopropylacrylamide) (PNIPAAM), one of the well-known thermosensitive polymers, has a lower critical solution temperature (LCST) in water at 32 °C.[16] This thermoresponsive property of PNIPAAM can be used to prepare thermoreversible separator, thermoresponsive soft actuator, automatic gel valve,[17] and smart, reusable catalysts.[18,19] Polylactides (PLA) are among the most important synthetic biodegradable polymers investigated for biomedical and pharmaceutical applications such as controlled drug delivery, resorbable sutures, medical implants, and scaffolds for tissue engineering.[20,21] The block copolymer of PNIPAAM and PLA should combine the thermosensitive property of PNIPAAM and biodegradable property of PLA together. The polymeric micelle formed from PNIPAAM conjugated to PLA polymer can improve the protein release pattern and maintain passive and thawing with targeting to tissue sites. Temperature change can alter the hydrophilicity and conformation of PNIPAAM. This may lead to changes in the physicochemical properties of microspheres, protein release rate, and biological behavior. Since PLA is biodegradable, the polymeric micelles formed from PNIPAAM conjugated to PLA will dissociate into homopolymer when the hydrophobic segment (PLA) is degraded. PNIPAAM (such as molecular weight <50 000) will exhibit no toxicity caused by long-term accumulation because it will be excreted by glomerular filtration.[22,23] However, there is still no efficient method to prepare amphiphilic block copolymer of PNIPAAM-*b*-PLA with well-defined structure and controlled molecular weight.

Since its discovery by Szwarc et al.[24] in 1956, living polymerization remains the main tool for polymer chemists to control molecular weight, composition, and architecture of polymer chains.[25] Many kinds of block copolymer have been prepared by the sequential (two-step) polymerization of corresponding monomers through living polymerization mechanism (e.g., living anionic, cationic procedures, stable free radical polymerization (SFRP), atom transfer radical polymerization (ATRP), reversible addition−fragmentation chain transfer (RAFT) polymerization)[26−34] or combination of two different polymerization mechanisms (such as ROP-ATRP,[34] ATRP-NMP,[35] and cationic-ATRP[36]). There is no successful experiment of synthesizing amphiphilic block copolymer of PNIPAAM and PLA with well-defined structure and controlled molecular weight by the living polymerization method until now. The traditional method to synthesize amphiphilic block copolymer of PNIPAAM and PLA is as shown in Scheme 1: First, hydroxy-terminated poly(*N*-isopropylacrylamide) precursor polymer was prepared by the radical polymerization using benzoyl peroxide (BPO) as the initiator and 2-hydroxyethanethiol as a chain transfer agent. Second, the diblock copolymers of PNIPAAM and PLA were synthesized by the ring-opening polymerization of lactide with the hydroxy-terminated PNIPAAM in toluene using tin(II) 2-ethylhexanoate as the catalyst.[23]

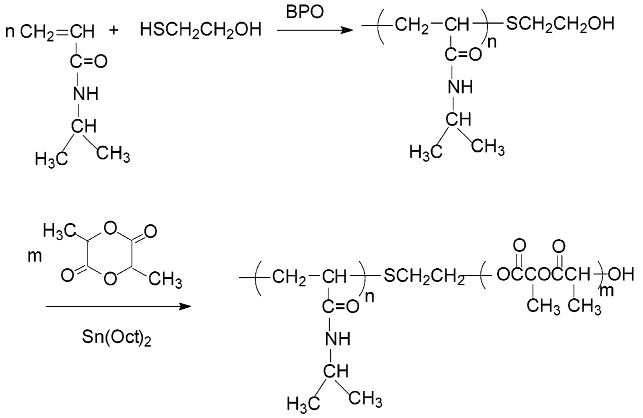
Here, we report a new method to prepare block polymers of PNIPAAM and PLA with well-defined

---

† Hefei University of Technology.
‡ University of Science and Technology of China.
* Corresponding author: e-mail 1yzyou@ustc.edu.

10.1021/ma048444t CCC: $27.50 © 2004 American Chemical Society
Published on Web 12/01/2004

Scheme 1



structure and controlled molecular weight by combination of two different polymerization mechanisms (ROP and RAFT methods) as shown in Scheme 2. First, we synthesized compound **1**, which has two hydroxy groups and a centered trithiocarbonate unit. Second, ring-opening polymerization of lactide with compound **1** under tin(II) 2-ethylhexanoate catalyst produced PLA with a trithiocarbonate unit located at the chain center. Third, RAFT polymerization of NIPAAM using this PLA with a centered trithiocarbonate unit as macromolecular transfer agent produced amphiphilic triblock copolymer of PNIPAAM and PLA with controlled molecular weight and well-defined structure.

Experimental Section

Materials Tetrahydrofuran (THF) was distilled from purple sodium benzophenone ketyl solutions. Toluene was refluxed with sodium under bubbling nitrogen gas and distilled. High-purity lactide (Aldrich, 98%) was purified by recrystallization from toluene and dried in a vacuum overnight at room temperature. The radical initiator, *N,N′*-azobis(isobutyronitrile) (AIBN, 98%, Aldrich) was recrystallized from ethanol. The *N*-isopropylacrylamide (NIPAAM) monomer (97%, courtesy of Kohjin Co., Japan) was purified by recrystallization in a benzene/*n*-hexane mixture. Tin(II) 2-ethylhexanoate, Sn(Oct)$_2$ (Aldrich, 95%), was dried twice by distillation with xylene under reduced pressure and finally subjected to a fractionated distillation in a vacuum of 10^{-3} mbar. Anionic exchange resin 717 was bought from Shanghai Chemical Reagent Co. 2-Hydroxyethyl-2′-bromobutyrate (HEBrB) was prepared from the esterification reaction of ethylene glycol and 2-bromobutyric acid and purified according to a published method.[37] The structure of HEBrB was verified by ^{1}H NMR spectrum, δ (TMS, ppm): 1.06 (t, 3H, CHBrCH$_2$C***H***$_3$), 2.08 (m, 2H, CHBrC***H***$_2$CH$_3$), 3.87 (t, 2H, CH$_2$C***H***$_2$OH), 4.21 (t, 1H, C***H***BrCH$_2$CH$_3$), 4.31 (t, 2H, COO C***H***$_2$CH$_2$).

Synthesis of *S,S′*-Bis(2-hydroxyethyl-2′-butyrate) Trithiocarbonate (BHBT). BHBT was prepared according to Scheme 3. The typical procedure is as follows. Anionic exchange resin 717 with Cl$^-$ form in a column was continuously washed with 5% NaOH solution at a rate of 5 mL/min for 12 h and then washed with deionized water until neutralized. The resin was dried at 60 °C in a vacuum oven until constant weight. The dried resin (10 g) was added into carbon disulfide (50 mL, 0.84 mol), which acts as both solvent and reactant, and stirred at room temperature for about 5 min. The color of resin turned from yellow to blood red due to the formation of CS$_3{}^{2-}$ on the polymeric support. Into this suspension, HEBrB (4.1 g, 20.0 mmol) was added, the mixture was stirred under reflux for 12 h, and the color of the solution turned gradually into yellow. After completion of the reaction, the mixture was filtered and washed with carbon disulfide. The filtrate was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to yield 0.98 g (yield is about 27%) of a viscous yellow liquid. ^{1}H NMR, δ (TMS, ppm): 1.06 (t, 6H, 2C***H***$_3$), 2.05 (q, 4H, 2C***H***$_2$CH$_3$), 3.85 (t, 4H, 2C***H***$_2$OH), 4.25 (t, 4H, 2COOC***H***$_2$), 4.80 (t, 2H, 2SC***H***(C$_2$H$_5$)-COO). FT-IR (neat, cm^{-1}): 1734 (C=O), 1064(C=S). Elemental analysis: C 42.2%, H 6.0%, S 26.1%.

Polymerization of Lactide. For run 1 in Table 1, the flask was filled with nitrogen gas, and *S,S′*-bis(2-hydroxyethyl-2′-butyrate) trithiocarbonate (BHBT) (1.0 mmol) and LA (20 mmol) in toluene were added into a 100 mL round-bottom flask equipped with a stir bar via a syringe. After a toluene solution of Sn(Oct)$_2$ (0.1 mmol) was added, the flask was capped with a rubber septa and evacuated (1 mmHg) through a needle for more than 1 h. The reaction flask was immersed in an oil bath at 115 °C, and lactide was melted with stirring. The reaction was continued for 24 h. After the reaction was quenched by the addition of 0.3 M acetic acid aqueous solutions, the reaction mixture was dissolved in chloroform, and the polymer was precipitated into *n*-hexane. The precipitated polymer was recovered by filtration and washed with cold methanol. After being dried in a vacuum at room temperature for 24 h, PLA was obtained in 95% yield. M_n(GPC) = 5390, M_w/M_n = 1.21. ^{1}H NMR, δ (TMS, ppm): 5.06(–C***H***(CH$_3$)–OCO–), 4.80(–C***H***–S–), 4.20 (–C***H***$_2$C***H***$_2$OCO–), 2.07(–C***H***$_2$CH$_3$), 1.60 (–CH-(C***H***$_3$)–OCO–), 1.08 (–CH$_2$C***H***$_3$).

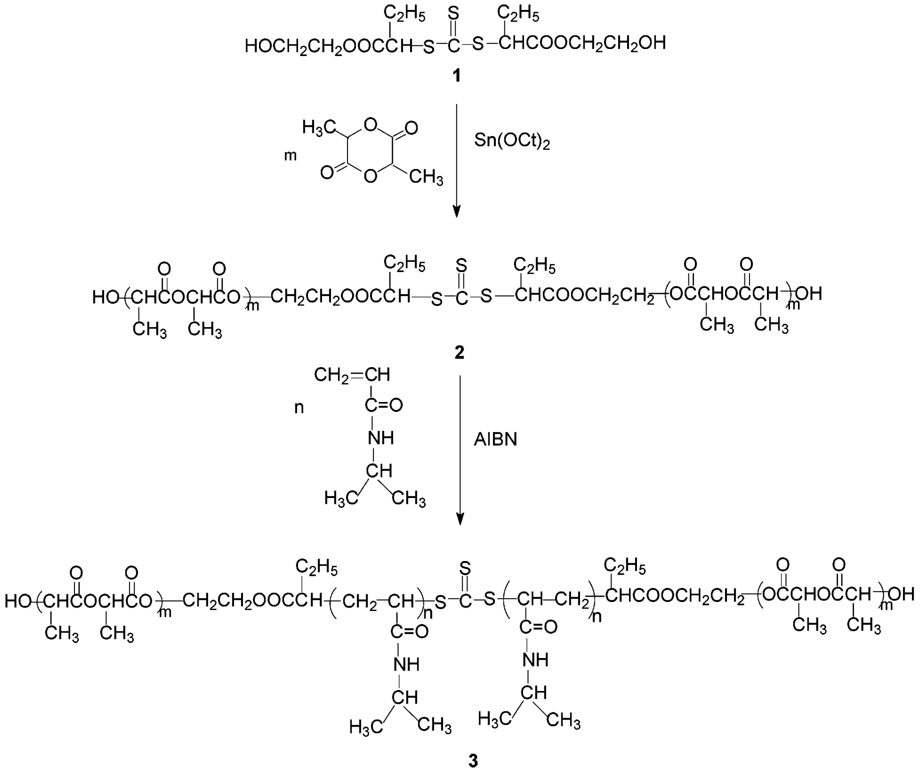
RAFT Polymerization of NIPAAM Using PLA with a Centered Trithiocarbonate Unit as RAFT Agent. For sample of PLA1–PNIPAAM1–PLA1, into a 5 mL polymerization tube with magnetic stirring bar, PLA1 [M_n(NMR) = 4970, 0.5 g, 0.1 mmol), AIBN (1.0 mg, 0.006 mmol), NIPAAM (3.0 g, 26 mmol), and THF (2 mL) were added, and then the tube was closed with three-way stopcocks. After being degassed by three freeze–vacuum–thaw cycles, the tube was sealed under vacuum and then immersed in an oil bath thermostated at 100 °C while stirring. After 10 h, the polymerization tube was cooled to room temperature rapidly, and the polymer was precipitated by pouring the solution in THF into *n*-hexane. After dried in a vacuum oven at 40 °C for 24 h, 1.36 g of triblock copolymer of PLA-*b*-PNIPAAM-*b*-PLA was obtained. M_n(GPC) = 20 780, M_w/M_n = 1.22. ^{1}H NMR, δ (TMS, ppm): 5.8–7.1 (–N***H***-CH–), 5.06 (–C***H***(CH$_3$)-OCO–), 4.0 (–NH–C***H***–), 1.2–2.5 (–C***H***$_2$C***H***–), 1.1 (–C***H***$_3$).

Characterization. NMR experiments were carried out on a Bruker 300 MHz nuclear magnetic resonance instrument using CDCl$_3$ as solvent and tetramethylsilane as internal reference. The FT-IR spectrum was obtained on a Bruker VECTOR-22 infrared spectrometer. Molecular weight and molecular weight distribution were determined on a Waters 150C gel permeation chromatograph (GPC) equipped with UltraStyragel columns (10^3, 10^4, and 10^5 Å) and 410 refractive index detector, using monodispersed polystyrene as calibration standard. THF was used as eluent at a flow rate of 1 mL/min. A Mettler Phototrode DP550 (λ = 550 nm) was used for transmission measurements on samples of ca. 0.3 wt %. Transmission was measured at temperature increments of 0.3 °C with equilibration times of 2 min. Transmission data were normalized to initial transmission at T = 25 °C. Sulfur content was determined on Elementar Co. Vario EL elemental analysis instrument.

Results and Discussion

Synthesis of *S,S′*-Bis(2-hydroxyethyl-2′-butyrate) Trithiocarbonate (BHBT). The polymerizations of NIPAAM and LA generally undergo two different polymerization mechanisms (free radical polymerization and ring-opening polymerization, respectively). To prepare the amphiphilic block copolymers of PNIPAAM and PLA with well-defined structure and controlled molecular weight, we should employ two different polymerization chemistries: living free radical polymerization and ROP methods. RAFT can control the polymerization of NIPAAM,[38] and the hydroxy group can act as initiating center for the ring-opening polymerization of lactide with Sn(Oct)$_2$ as catalyst. Thus, we should prepare a

Scheme 2



Scheme 3

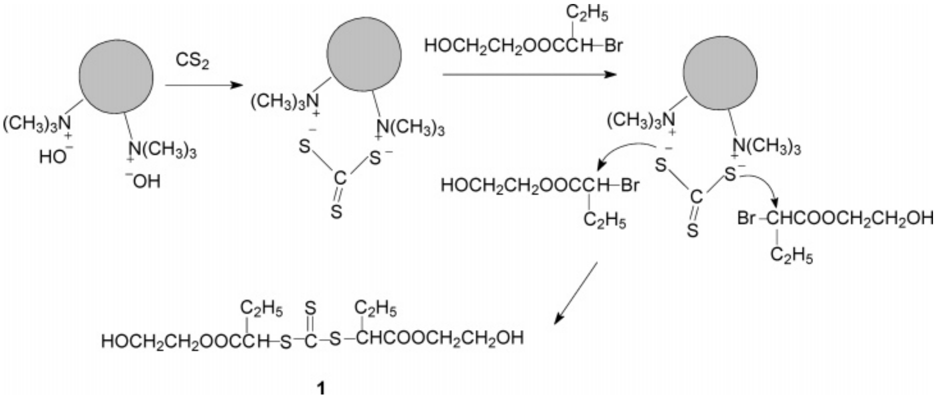


Table 1. Results of Ring-Opening Polymerization of Lactide (LA) with *S,S′*-Bis(2-hydroxyethyl-2′-butyrate) Trithiocarbonate (BHBT) as Initiator[a]

run	$[M]_0/[I]_0$	conv[b] (%)	S content[c] (%)	M_n ($\times 10^3$) NMR[d]	th[e]	GPC[f]	M_w/M_n[f]
1	20	95.0	2.932	3.21	3.10	5.39	1.21
2	30	91.0	1.868	4.97	4.30	7.88	1.18
3	60	97.0	0.890	10.66	8.75	14.61	1.25

[a] The polymerization was carried out at 115 °C for 24 h. BHBT was used as initiator; $[Sn(Oct)_2]_0:[LA]_0 = 1:200$ (molar ratio). [b] Determined by the gravimetry method. [c] Determined from elemental analysis. [d] NMR number-average molecular weight (M_n(NMR) calculated by $M_n(NMR) = (3\boldsymbol{I}_{5.06}/2\boldsymbol{I}_{1.08}) \times 144 + 370$. [e] Theory number-average molecular weight, M_n(th), was calculated according to $M_n(th) = ([M]_0/[I]_0) \times \text{conversion (\%)} \times 144 + 370$, where $[M]_0$ and $[I]_0$ are the initial concentrations of LA and BHBT and 144 and 370 are the molecular weights of LA and BHBT, respectively. [f] GPC number-average molecular weight, M_n(GPC), measured by GPC.

compound not only containing a thioester group but also containing a hydroxy group; the thioester group can control the polymerization of NIPAAM by the RAFT method, and the hydroxy group can act as initiating center for ring-opening polymerization of LA. Very few syntheses of thioesters containing hydroxy group have been reported although there have been many kinds of dithioester or trithioester prepared.[39] On the basis of previous experiments,[40] we synthesized trithioester containing two ending hydroxyl groups by using anion-exchange resin. The nucleophilic substitution reactions of CS_3^{2-} on polymeric supports with HEBrB produced *S,S′*-bis(2-hydroxyethyl-2′-butyrate) trithiocarbonate (BHBT), which has two ending hydroxy groups and a centered trithiocarbonate. The structures of the compound obtained were characterized by ^{1}H NMR and FT-IR; the results verified that the nucleophilic substitution reactions of CS_3^{2-} with HEBrB took place to form *S,S′*-bis(2-hydroxyethyl-2′-butyrate) trithiocarbonate (BHBT). In its ^{1}H NMR spetrum (Figure 1), the integral ratios of **e**:**d**:**c**:**b**:**a** are 1:1.94:1.98:2.09:3.10 (**e** corresponding to methine proton next to trithiocarbonate unit, **d** is ascribed to ester methylene protons, **c** corresponding to hydroxy methylene protons, **b** is assigned to methylene protons next to methyl group, and **a** corresponding to

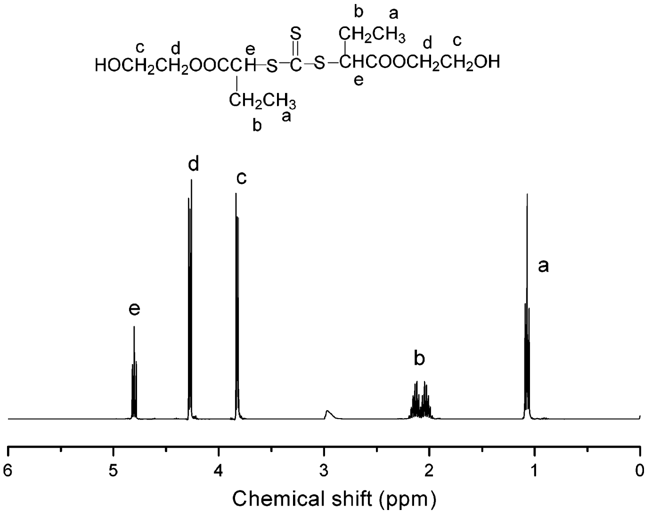


Figure 1. ^{1}H NMR spectrum of *S*,*S*′-bis(2-hydroxyethyl-2′-butyrate) trithiocarbonate.

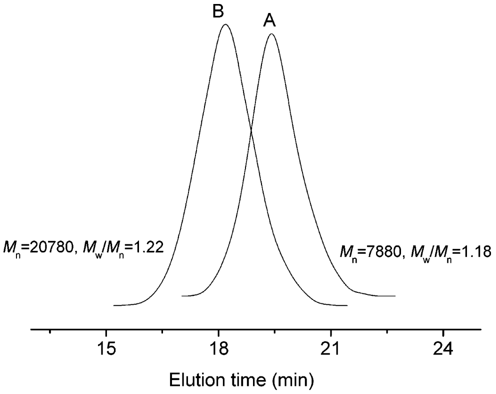


Figure 2. GPC traces of PLA−SC(S)S−PLA (A) and triblock copolymer of PLA-*b*-PNIPAAM-*b*-PLA (B) formed from RAFT polymerization of NIPAAM using PLA−SC(S)S−PLA (M_n = 7880) as macro-transfer agent.

methyl protons), which indicates that each product molecule contains two ending hydroxy groups.

Ring-Opening Polymerization of LA. Compound **1** contains two hydroxy groups which can be used as the initiating centers for the ring-opening polymerization of lactide with Sn(Oct)$_2$ as catalyst. Polymerizations of lactide under different reaction conditions (runs 1−3) are summarized in Table 1. All of the polymers obtained have narrow molecular weight distributions. A typical GPC curve of the polymer obtained is shown in Figure 2. This curve is unimodel and symmetric, which is similar to the previous experiment.[41]

The chemical structures of the polymers produced were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy. In the ^{13}C NMR spectrum (Figure 3) of the PLA prepared by using **1** as initiator with Sn(Oct)$_2$ as catalyst, the peaks of C=O and C−O are located at δ = 171.4 and 69.8 ppm, respectively. In the ^{1}H NMR spectrum of PLA (Figure 4), apart from the strong signals coming from the PLA chain (C$\boldsymbol{H}_3$ protons centered at δ = 1.60 ppm and C*H* proton centered at δ = 5.06 ppm), small peaks at δ = 1.08, 2.07, 4.20, and 4.80 ppm ascribed to the methyl protons (−CH$_2$C$\boldsymbol{H}_3$), methylene protons (−C$\boldsymbol{H}_2$CH$_3$), ester methylene protons [−C(S)SCHCOOC$\boldsymbol{H}_2$C$\boldsymbol{H}_2$OCOPLA], and methine proton [−C(S)S−C$\boldsymbol{H}$COO] next to trithiocarbonate unit originating from compound **1**, respectively, also appeared, which indicates that compound **1** participated in the

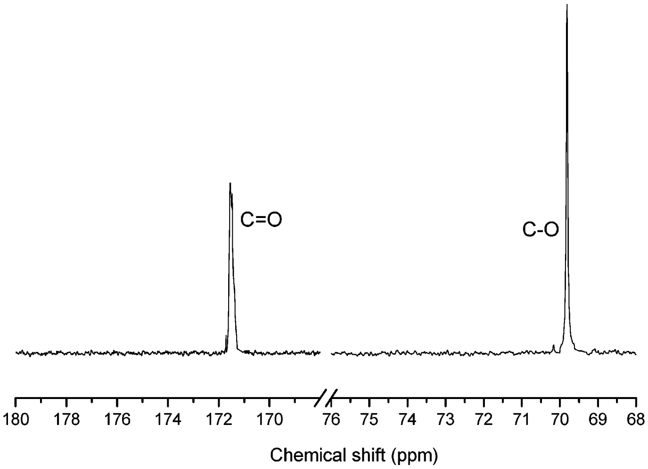


Figure 3. ^{13}C NMR spectrum of PLA−SC(S)S−PLA with M_n(GPC) of 7880 and M_w/M_n = 1.18.

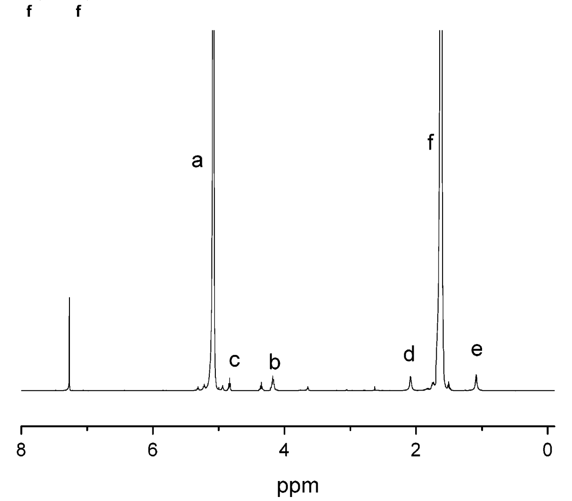


Figure 4. ^{1}H NMR spectrum of PLA−SC(S)S−PLA with M_n(GPC) of 7880 and M_w/M_n = 1.18.

initiating polymerization of LA and the trithiocarbonate unit remained in PLA chain. The sulfur contents in PLA obtained from elementary experiment are listed in Table 1, which are similar to the sulfur contents obtained by ^{1}H NMR method [S % = 96/M_n(NMR) × 100%], indicating that almost each PLA macromolecule contains trithiocarbonate unit at the center.

Preparation of Amphiphilic Triblock Copolymers of PLA and PNIPAAM from RAFT Polymerization of NIPAAM. Several kinds of well-defined triblock copolymers have been successfully prepared by RAFT polymerization of the second monomer using macromolecules with trithiocarbonate group in the chain center as macro-chain-transfer agent.[42] Previous experimental results show that the RAFT polymerization of NIPAAM is a living free radical polymerization.[38] Therefore, the RAFT polymerization of NIPAAM with PLA−SC(S)S−PLA as macro-transfer agent will produce well-defined triblock copolymer, PLA-*b*-PNIPAAM-*b*-PLA. During the RAFT polymerization of NIPAAM, we used the GPC to trace the polymerization; GPC curve analyses exhibited a decrease in retention time for the formed triblock copolymer of PLA-*b*-PNIPAAM-*b*-PLA relative to the original PLA macromolecular RAFT

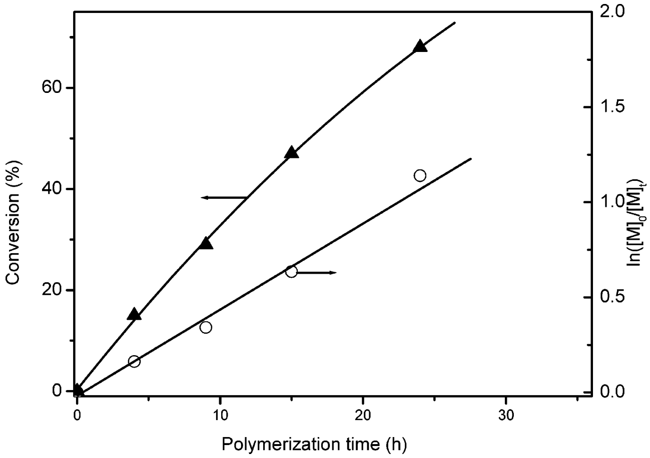


Figure 5. Relationships of conversion and $\ln([M]_0/[M]_t)$ with polymerization time in the RAFT polymerization of NIPAAM using PLA−SC(S)S−PLA (M_n(GPC) = 7880, M_w/M_n = 1.18) as macro-chain-transfer agent.

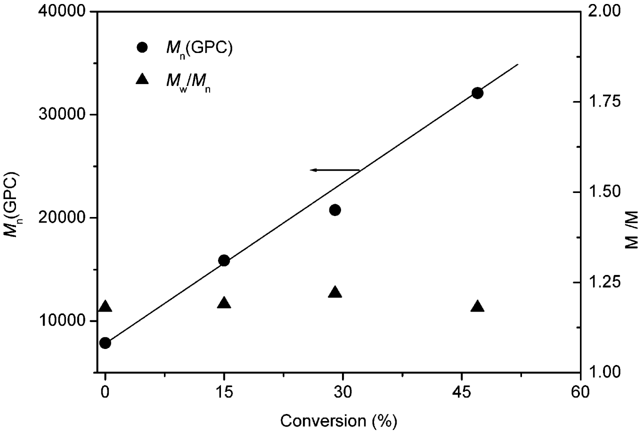


Figure 6. Plots of M_n(GPC) and M_w/M_n with NIPAAM conversion in the RAFT polymerization of NIPAAM using PLA−SC(S)S−PLA (M_n(GPC) = 7880, M_w/M_n = 1.18) as macro-chain-transfer agent.

agent, indicating that NIPAAM was inserted into the polymer chain between the trithiocarbonate unit and PLA with small change in molecular weight distribution (M_w/M_n). For verifying that the growth of the NIPAAM block via RAFT polymerization was controlled, the polymerizations of NIPAAM were monitored; both $\ln([M]_0/[M]_t)$ vs polymerization time and M_n vs percent conversion were plotted and shown in Figure 5 and Figure 6, respectively. $\ln([M]_0/[M]_t)$ exhibited linearly increasing with polymerization time, M_n developed linearly with the increase of monomer conversion, and molecular weight distribution (M_w/M_n) remained low (<1.3) throughout the RAFT polymerization of NIPAAM. All these facts are consistent with a controlled or living process, and the chain length of PNIPAAM can be controlled.

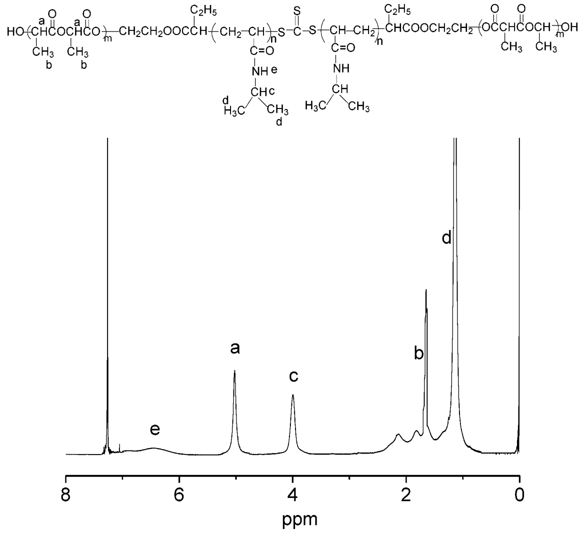


Figure 7. ^{1}H NMR spectrum of triblock copolymer of PLA-*b*-PNIPAAM-*b*-PLA with M_n(GPC) of 20 780.

The chemical structures of the formed triblock copolymers of PLA-*b*-PNIPAAM-*b*-PLA were analyzed by ^{1}H NMR. Figure 7 is the typical ^{1}H NMR spectrum of the PLA-*b*-PNIPAAM-*b*-PLA. Besides the signals of PLA blocks (C$\boldsymbol{H}_3$ protons centered at δ = 1.62 ppm and C$\boldsymbol{H}$ proton centered at δ = 5.06 ppm), characteristic signals of PNIPAAM (such as δ = 4.0 ppm ascribed to the methine proton of isopropyl unit, δ = 1.2−2.5 ppm ascribed to methylene and methine protons in the main chain of PNIPAAM, δ = 1.10 ppm assigned to methyl protons of isopropyl units) also appeared in Figure 7, which further verifies the formation of PLA-*b*-PNIPAAM-*b*-PLA. From Table 2, we can see that PNIPAAM content in triblock copolymers and M_n(NMR) of the triblock copolymers obtained increased with the increase of polymerization time. Because the M_n(GPC) based on using monodispersed polystyrene as calibration standards cannot exhibit the true molecular weight of PLA-*b*-PNIPAAM-*b*-PLA, we used the ^{1}H NMR method to characterize the molecular weight [M_n(NMR)] of PLA-*b*-PNIPAAM-*b*-PLA based on eq 1.

$$M_n(\mathrm{NMR}) = M_{n\mathrm{PLA}}(\mathrm{NMR}) + \frac{M_{n\mathrm{PLA}}(\mathrm{NMR})}{144} \times \frac{2I_{4.0}}{I_{5.06}} \times 113 \quad (1)$$

where $M_{n\mathrm{PLA}}$(NMR) is the molecular weight of PLA obtained from ^{1}H NMR method; 144 and 113 are the molecular weights of LA and NIPAAM, respectively; $I_{4.0}$ and $I_{5.06}$ are the integral values of the peaks at δ = 4.0 ppm (the methine protons of isopropyl unit in PNIPAAM) and 5.06 ppm (the methine protons of PLA). The calculated results are listed in Table 2. M_n(NMR) and M_n(th) were smaller than M_n(GPC), which may result

Table 2. Characteristics of PLA−PNIPAAM−PLA[a]

run	reaction time (h)	conv (%)	PLA/PNIPAAM	M_n(GPC)	M_n(th)[b]	M_n(NMR)[c]	M_w/M_n	LCST (°C)
PLA1				7 880	4 300	4 970	1.18	
PLA1−PNIPAAM1−PLA1	9	29	1.0/1.90	20 780	11 780	12 380	1.22	31.3
PLA1−PNIPAAM2−PLA1	15	47	1.0/3.02	32 110	16 430	16 748	1.19	31.0
PLA1−PNIPAAM3−PLA1	19	55	1.0/3.6	40 980	18 490	19 010	1.29	31.1
PLA2				5 390	3 210	3 100	1.21	
PLA2−PNIPAAM1−PLA2	9	25.4	1.0/1.70	15 200	8 110	7 980	1.30	31.4

[a] The weights of PLA, NIPAAM, and AIBN added are 0.5 g, 3.0 g, and 1.0 mg, respectively. [b] Calculated by $M_n(\mathrm{th}) = M_{n\mathrm{PLA}}(\mathrm{th}) + M_{n\mathrm{PLA}}(\mathrm{th}) \times (3.0/0.5) \times \mathrm{conv}$ (%). [c] Calculated by $M_n(\mathrm{NMR}) = M_{n\,\mathrm{PLA}}(\mathrm{NMR}) + [M_{n\,\mathrm{PLA}}(\mathrm{NMR})/144\,] \times (2\boldsymbol{I}_{4.0}/\boldsymbol{I}_{5.06}) \times 113$.

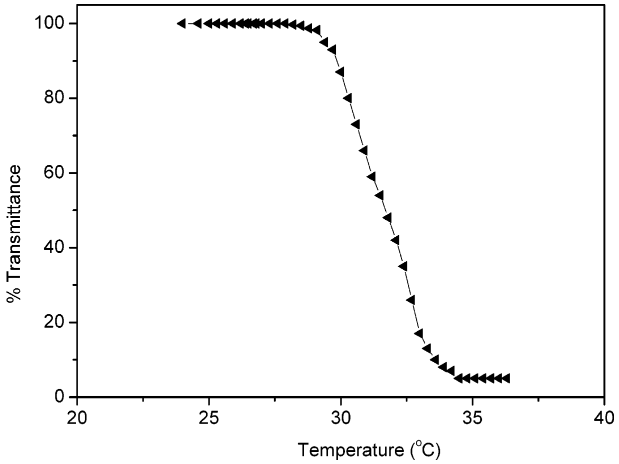


Figure 8. Transmittance changes of PLA-*b*-PNIPAAM-*b*-PLA (M_n(GPC) = 20 780) aqueous solution as a function of temperature.

from using monodispersed polystyrene as standards in GPC measurement; however, M_n(NMR) agreed with M_n(th) well, indicating that M_n(NMR) is similar to the true molecular weight.

Optical Transmittance. It is known that the conformation and solubility of PNIPAAM chains in water can change with temperature. PNIPAAM homopolymer chains could collapse to global state from coil state at $T > 32$ °C due to that in this temperature range,[16−19] water is a very poor solvent for PNIPAAM chains. This is because that at temperatures below the LCST, the predominantly intermolecular hydrogen bonding between the PNIPAAM chains and water molecules make the PNIPAAM chains soluble in water and is of coil structure, while at temperatures above the LCST, intramolecular hydrogen bonding between C=O and N−H groups in the PNIPAAM chains results in a compact and collapsed conformation of PNIPAAM chains, which makes it difficult for PNIPAAM chain soluble in water. Aqueous solution of PLA-*b*-PNIPAAM-*b*-PLA copolymers made by the dialysis method[43] indeed underwent a change in their structure at the temperature corresponding to the LCST of about 31 °C, as shown in Figure 8. These LCSTs were determined by the temperature showing onset of turbidity in a copolymer solution. The concentration of this solution was determined to be 0.3 wt %. LCST values for the PLA-*b*-PNIPAAM-*b*-PLA aqueous solution are listed in Table 2, and the PNIPAAM chain length has no distinct effect on LCST.

Summary

S,*S*′-Bis(2-hydroxyethyl-2′-butyrate) trithiocarbonate (BHBT), which has two hydroxy groups and a centered trithiocarbonate group, was successfully synthesized by the nucleophilic substitution reactions of CS_3^{2-} with HEBrB on the polymeric supports. Two hydroxy groups in BHBT were used as two initiating centers in the ROP of lactide to form PLA with a centered trithiocarbonate. The thermally sensitive and biodegradable block copolymers of PLA-*b*-PNIPAAM-*b*-PLA were successfully synthesized by RAFT polymerization of NIPAAM using PLA with a centered trithiocarbonate unit as RAFT agent. The results of ^{1}H NMR and GPC show that the thermally sensitive and biodegradable block copolymers of PLA-*b*-PNIPAAM-*b*-PLA have well-defined structure, controlled molecular weight, and narrow molecular weight distribution. The aqueous solution of the block copolymer has a LCST around 31 °C. The properties of this thermally sensitive and biodegradable block copolymer system will be very interesting from both applied and fundamental perspectives, particularly for active targeting as drug carrier, drug release.

Acknowledgment. The authors thank the support from the Nation Natural Science Foundation of China under Contract No. 20404003.

References and Notes

(1) Goldacker, T.; Abetz, V.; Stadler, R.; Erukhimovich, I.; Leibler, L. *Nature (London)* **1999**, *398*, 137.
(2) Thomas, E. L. *Science* **1999**, *286*, 1307.
(3) Gido, S. P.; Thomas, E. L. *Macromolecules* **1997**, *30*, 3739.
(4) Bates, F. S.; Fredrickson, G. *Phys. Today* **1999**, *32*, 38.
(5) Goldacker, T.; Abetz, V. *Macromolecules* **1999**, *32*, 5165.
(6) Tuzar, Z.; Kratochvil, P. *Adv. Colloid Interface Sci.* **1976**, *6*, 201.
(7) Yokoyama, M. *Ther. Drug Carrier Syst.* **1992**, *9*, 213.
(8) Wilhelm, M.; Zhao, C. L.; Wang, Y. C.; Xu, R. L.; Winnik, M. A.; Mura, J. L.; Riess, G.; Croucher, M. D. *Macromolecules* **1991**, *24*, 1033.
(9) Jeong, B.; Bae, Y. H.; Lee, D. S.; Kim, S. W. *Nature (London)* **1997**, *388*, 860.
(10) Zhang, W. Q.; Shi, L. Q.; An, Y. L.; Gao, L. C.; Wu, K.; Ma, R. J. *Macromolecules* **2004**, *37*, 2551.
(11) Matsumoto, K.; Mazaki, H.; Matsuoka, H. *Macromolecules* **2004**, *37*, 2256.
(12) Matejicek, P.; Humpolickova, J.; Prochazka, K.; Tuzar, Z.; Spirkova, M.; Hof, M.; Webber, S. E. *J. Phys. Chem. B* **2003**, *107*, 8232.
(13) Bes, L.; Angot, S.; Limer, A., Haddleton, D. M. *Macromolecules* **2003**, *36*, 2493.
(14) Matsumoto, K.; Mazaki, H.; Nishimura, R.; Matsuoka, H.; Yamaoka, H. *Macromolecules* **2000**, *33*, 8295.
(15) Nakano, M.; Deguchi, M.; Matsumoto, K.; Matsuoka, H.; Yamaoka, H. *Macromolecules* **1999**, *32*, 7437.
(16) (a) Schild, H. G. *Prog. Polym. Sci.* **1992**, *17*, 163. (b) Senff, H.; Richtering, W. *Colloid Polym. Sci.* **2000**, *278*, 830. Hu, T.-J.; You, Y.-Z.; Pan, C.-Y.; Wu, C. *J. Phys. Chem. B* **2002**, *106*, 6659.
(17) Bhattacharya, A. *Prog. Polym. Sci.* **2000**, *25*, 371.
(18) Bergbreiter, D. E.; Koshti, N.; Franchina, J. G.; Frels, J. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 1040.
(19) Bergbreiter, D. E.; Caraway, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 6092.
(20) Chiellini, E.; Solaro, R. *Adv. Mater.* **1996**, *8*, 305.
(21) Uhrich, K. E.; Cannizzaro, S. M.; Langer, R. S.; Shakesheff, K. M. *Chem. Rev.* **1999**, *99*, 3181.
(22) Cammas, S.; Suzuki, K.; Sone, C.; Sakurai, Y.; Kataoka, K.; Okano, T. *J. Controlled Release* **1997**, *48*, 157.
(23) Kohori, F.; Sakai, K. Aoyagi, T.; Yokoyama, M.; Sakurai, Y.; Okano, T. *J. Controlled Release* **1998**, *55*, 87.
(24) Szwarc, M.; Levy, M.; Milkovich, R. *J. Am. Chem. Soc.* **1956**, *78*, 2656.
(25) Webster, O. W. *Science* **1991**, *251*, 887.
(26) (a) Hawker, C. J. *J. Am. Chem. Soc.* **1994**, *116*, 11185. (b) Hawker, C. J. *Trends Polym. Sci.* **1996**, *4*, 183.
(27) (a) Kato, M.; Kamigaito, M.; Sawamoto, M.; Higashimura, T. *Macromolecules* **1995**, *28*, 1721. (b) Wang, J. S.; Matyjaszewski, K. *J. Am. Chem. Soc.* **1995**, *117*, 5614. (c) Patten, T. E.; Xia, J.; Abernathy, T.; Matyjaszewski, K. *Science* **1996**, *272*, 866.
(28) Mayadunne, R. T. A.; Rizzardo, E.; Chiefari, J.; Chong, Y. K.; Moad, G.; Thang, S. H. *Macromolecules* **1999**, *32*, 6977.
(29) Barner-Kowollik, C.; Davis, T. P.; Heuts, J. P. A.; Stenzel, M. H.; Vana, P.; Whittaker, M. J. *J. Polym. Sci., Polym. Chem.* **2002**, *41*, 365.
(30) Vana, P.; Quinn, J. F.; Davis, T. P.; Barner-Kowollik, C. *Aust. J. Chem.* **2002**, *55*, 425.
(31) Mayadunne, R. T. A.; Jeffery, J.; Moad, G.; Rizzardo, E. *Macromolecules* **2003**, *36*, 1505.
(32) Dureault, A.; Gnanou, Y.; Taton, D.; Destarac, M.; Leising, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 2869.
(33) Bai, R.-K.; You, Y.-Z.; Pan, C.-Y. *Polym. Int.* **2000**, *49*, 898.
(34) Mecerreyes, D.; Moineau, G.; Dubois, P.; Jérôme, R.; Hedrick, J. L.; Hawker, C. J.; Malmström, E. E.; Trollsas, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1274.

(35) Tunca, U.; Karliga, B.; Ertekin, S.; Ugur, A. L.; Sirkecioglu, O.; Hizal, G. *Polymer* **2001**, *42*, 8489.

(36) Bernaerts, K. V.; Schacht, E. H.; Goethals, E. J.; Du Prez, F. E. *J. Polym. Sci., Part A: Polym. Chem.* **2003**, *41*, 3206.

(37) Xu, Y. J.; Pan, C. Y.; Tao, L. *J. Polym. Sci., Part A: Polym. Chem.* **2000**, *38*, 436.

(38) (a) Ganachaud, F.; Monteiro, M. J.; Gilbert, R. G.; Dourges, M. A.; Thang, S. H.; Rizzardo, E. *Macromolecules* **2000**, *33*, 6738. (b) Schilli, C.; Lanzendörfer, M. G.; Müller, A. H. E. *Macromolecules* **2002**, *35,* 6819.

(39) Le, T. P.; Moad, G.; Rizzardo, E.; Thang, S. H. In PCT Int. Appl. WO 9801478 A1 980115, 1998.

(40) (a) Tamami, B.; Kiasat, A. R. *J. Chem. Res. (S)* **1998**, 454. (b) Bai, R.-K.; You, Y.-Z.; Pan, C.-Y. *Macromol. Rapid Commun.* **2001**, *22*, 315.

(41) Tao, L.; Luan, B.; Pan, C.-Y *Polymer* **2003**, *44*, 1013.

(42) (a) Liu, J.; Hong, C.-Y.; Pan, C.-Y. *Polymer* **2004**, *45*, 4413. (b) Mayadunne, R. T. A.; Rizzardo, E.; Chiefari, J.; Krstina, J.; Moad, G.; Postma, A.; Thang, S. H. *Macromolecules* **2000**, *33*, 243.

(43) Chung, J. E.; Yokoyama, M.; Okano, T. *J. Controlled Release* **2000**, *65*, 93.

MA048444T